KINETICAL DATA TO ACYL MIGRATION N→O

By Á. FURKA

Institute of Applied Chemistry, The University, Szeged

(Received March 14, 1959)

The rate of rearrangement of (±) cis- and trans-2-benzamido-cyclohexan-1-ol on the effect of hydrogen chloride in dry dioxan at 71° C, 81° C and 91° C was measured. From data of measurements the rate constants of the reactions and also their activation energies were calculated.

The rearrangement of 2-acylamido-alcohols into 0-acyl-2-aminoalcohols due to the effect of acids and the revelsal of this process in alkali media are long well known [1]—[5]. In order to elucidate the mechanism of the process, kinetical investigations were carried out by WELSH [6] and MCCASLAND [7]. The former followed the rearrangement of N-acyl-ephedrine on the effect of hydrochloric acid in ethanol, back-titrating the excess of acid, while the latter investigated the change of 2-acetamino-cyclohexanols using water as solvent, so that the nitrogen content of the compound formed during the rearragement was determined by VAN SLYKE's method.

This paper contains data obtained by the author's investigation on the rearrangement of (±) cis- and trans-2-benzamido-cyclohexan-1-ol. Measurements were carried out in dry dioxan in presence of 8—60 times excess of hydrogen chloride, at 71° C, 81° C and 91° C. Dry dioxan was chosen

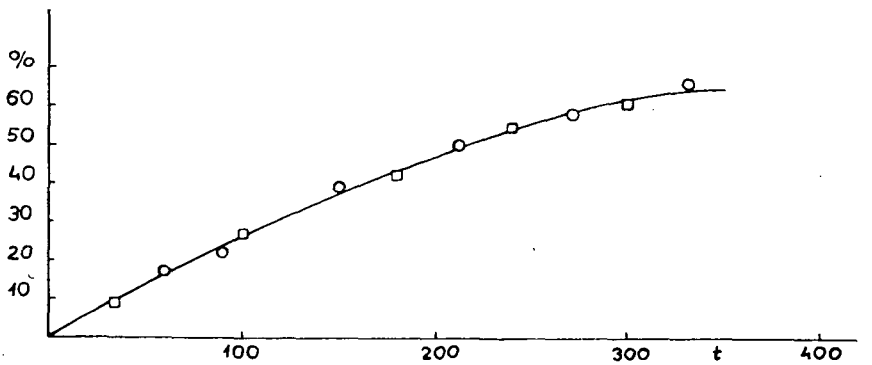

Fig. 1. □ : $a = 0{,}100$; $b = 1{,}4363$ (temp. = 71° C)
○ : $a = 0{,}050$; $b = 0{,}7810$

as solvent in order to avoid side processes which may take place on the effect of water (*e. g.* hydrolysis of O-benzoyl compound). The great excess of hydrogen chloride mentioned above was claimed by the fact that cis modification has only a slight solubility in dioxan containing less HCl than it was applied. It seemed reasonable to study the rearrangement of trans modification also at such hydrogen chloride concentration. The process was followed by the determination of primer aminonitrogen. Deductions concerning the mechanism of the process, made on the basis of these and É. FODOR—VARGA's measurements [8] had been published [9].

Results[1]

Rearrangement of (±) *trans-2-benzamido-cyclohexan-1-ol*

It has been attempted to determine the order of the reaction by several methods. Fig. 1 shows that 2-fold change in the volume of the solvent has no effect on the rate of formation of the end-product when expressed it in per cent of the initial quantity of starting material. This indicates that the reaction may be of first order.

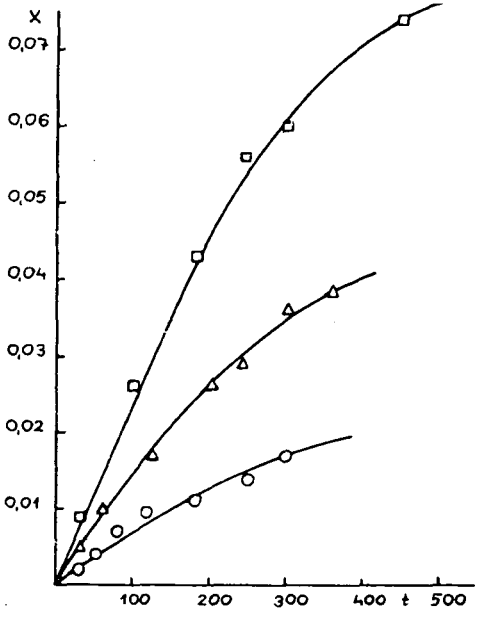

Fig. 2.
○ : $a = 0{,}025$; $b = 1{,}2754$ (temp. = 71° C)
△ : $a = 0{,}050$; $b = 1{,}4721$
□ : $a = 0{,}100$; $b = 1{,}4363$

Further it was investigated how the rate of formation of the end-product depends — at nearly the same initial hydrogen chloride concentrations — on the initial concentration of substrate (Fig. 2). Plotting the logarithms of initial rates, graphically determined, against the logarithms of concentrations, with good approximation, a straight line was obtained. The order referred to the substrate was obtained from the slope of this plot giving a value of about 0,8.

In order to determine the partial order referred to hydrogen chloride it was examined how the changes of the initial concentration of hydrogen chloride influence the rate of rearrangement (Fig. 3). The figure illustrates that the rate of rearrangement increases only to a very small extent with the increase of the hydrogen chloride concentration. The extent of the increase was not sufficient for the graphical determination

[1] Symbols: a — initial concentration of substrate, x — concentration of substrate, b — initial concentration of hydrogen chloride
Units: concentration — mole/l, time — minute, rate constant — l. mol.$^{-1}$·min.$^{-1}$.

of partial order referred to hydrogen chloride, *i. e.* to yield values strictly differing from zero.

Each data, shown above, indicate that the process is of first order. However, there are data suggesting that the existence of the first order found is not sufficiently proved. On the one hand, hydrogen chloride was applied, from practical viewpoints, in great excess, and this may cause the result obtained at the determination of partial order of hydrogen chloride to be doubtful. Here it may be mentioned that É. FODOR—VARGA [8] in a series of measurements carried out with the same model — in the course of which the initial hydrogen chloride concentration was investigated at a wider range (measurements were performed with back-titrating of the excess of hydrogen chloride) — found the partial order of hydrogen chloride to be almost unit. At the same time constants found by her and calculated from second order equations show a better agreement than those calculated from first order equations. Table I contains some data which illustrate that in measurements carried out by the author the values of rate constants (k_2) calculated according to second order do not show in every case worse agreement than those calculated according to first order (k_1).

It must be noted that some difficulties arise from the fact that the activity coefficients referring to dioxan solution are not known, thus in the calculations instead of them the concentrations were used. On the other hand when calculating activation energies it became apparent that values obtained from k_2 instead of k_1 do not show considerable difference.

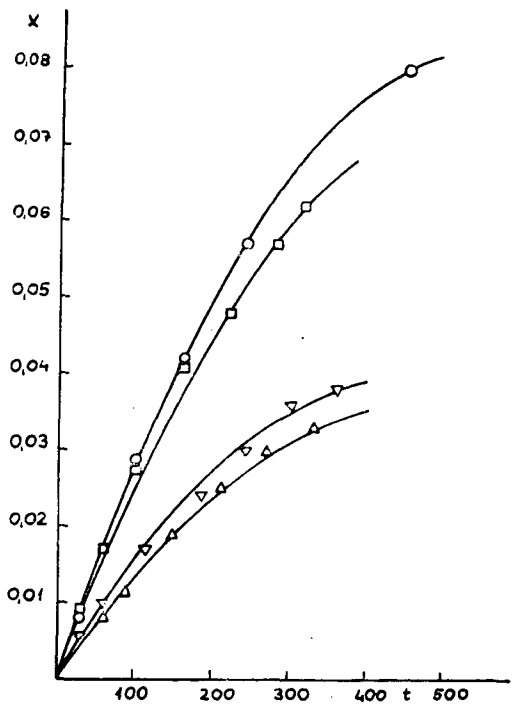

Fig. 3.

□ : $a = 0{,}100$; $b = 1{,}0330$ (temp. = 71° C)
○ : $a = 0{,}100$; $b = 1{,}4363$
△ : $a = 0{,}050$; $b = 0{,}7810$
▽ : $a = 0{,}050$; $b = 1{,}4721$

Fig. 4 shows results of measurements at different temperatures. It is seen that as the temperature rises there is a marked increase in the rate of acyl migration. The value of activation energy, evaluated from dependence of rate constants on the temperature is 18.5 Kcal/mole.

Further it was investigated how the presence of water influences the rate of the process. To dioxan containing hydrogen chloride, 2% of water was added, then the initial substance was solved in it. The dissolving was

Table I

$a = 0{,}100$ $b = 1{,}436$ temp. $= 71°C$		$a = 0{,}050$ $b = 0{,}781$ temp. $= 71°C$		$a = 0{,}050$ $b = 1{,}514$ temp. $= 71°C$		$a = 0{,}050$ $b = 0{,}847$ temp. $= 81°C$		$a = 0{,}050$ $b = 1{,}751$ temp. $= 91°C$	
$k_1 \cdot 10^3$	$k_2 \cdot 10^3$	$k_1 \cdot 10^3$	$k_2 \cdot 10^3$	$k_1 \cdot 10^3$	$k_2 \cdot 10^3$	$k_1 \cdot 10^3$	$k_2 \cdot 10^3$	$k_1 \cdot 10^3$	$k_2 \cdot 10^3$
2,97	2,08	3,16	4,06	2,80	2,32	6,08	7,22	17,94	10,27
3,22	2,26	2,90	3,83	3,02	2,00	5,52	6,57	19,17	11,50
3,19	2,25	3,17	4,14	3,90	2,59	5,70	6,79	19,04	10,93
3,38	2,37	3,30	4,30	4,12	2,74	5,84	7,00	19,73	10,82
3,23	2,31	3,34	4,40	4,27	2,85	5,69	6,83	19,02	10,95
3,01	2,16	3,30	4,33	3,95	2,64	5,87	7,08	18,84	10,90

Table II

temp. °C	a	b	H_2O %	$k_1 \cdot 10^3$	$k_2 \cdot 10^3$
71	0,100	1,033	—	3,17	3,53
71	0,100	1,436	—	3,33	2,26
71	0,050	0,780	—	3,19	4,18
71	0,050	0,997	—	3,11	3,14
71	0,050	1,514	—	3,68	2,52
71	0,025	1,275	—	3,53	2,77
71	0,100	0,893	2	1,82	2,06
81	0,100	0,924	—	6,11	6,80
81	0,100	1,440	—	7,51	5,34
81	0,050	0,847	—	5,78	6,91
91	0,100	1,040	—	12,67	12,41
91	0,100	1,507	—	17,09	11,54
91	0,050	1,751	—	18,96	10,69
91	0,025	1,346	—	15,56	11,52

Table III

$a = 0{,}050$ $b = 1{,}782$ temp. $= 71°C$		$a = 0{,}050$ $b = 1{,}786$ temp. $= 81°C$		$a = 0{,}050$ $b = 1{,}765$ temp. $= 91°C$	
$k_1 \cdot 10^3$	$k_2 \cdot 10^3$	$k_1 \cdot 10^3$	$k_2 \cdot 10^3$	$k_1 \cdot 10^3$	$k_2 \cdot 10^3$
16,08	8,66	34,13	19,19	58,85	38,00
14,77	8,33	34,75	19,66	57,91	33,04
18,87	10,70	37,79	21,40	58,70	33,67
16,37	9,29	35,67	20,30	59,36	33,96
17,02	9,70	40,53	23,15	59,97	34,43
16,10	9,17	38,28	21,91	58,03	33,38
16,53	9,31	36,85	20,93	58,80	34,41
16,53	9,31	36,85	20,93	58,80	34,41

not perfect, an opalescent solution was obtained. Fig. 5 shows that water content of 2 % resulted in a considerable decrease of the rate of rearrangement.

The mean values of rate constants calculated from measurements, carried out at different temperatures and initial concentrations are summarized in Table II. It can be seen that k_1 values in general increase with the increase of concentration of hydrogen chloride, while k_2 values decrease. This indicates that the real value of the order of overall reaction is about between 1 and 2 and this refers — together with facts mentioned above — to the existence of a more complex process.

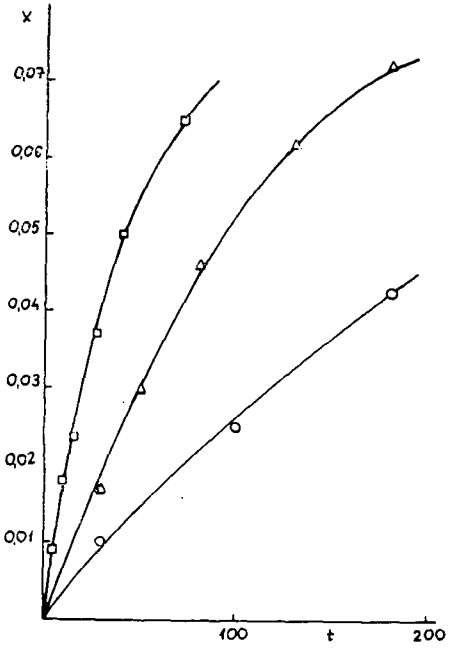

Fig. 4.

○ : $a = 0{,}100$; $b = 1{,}4363$; temp. = 71° C
△ : $a = 0{,}100$; $b = 1{,}4404$; temp. = 81° C
□ : $a = 0{,}100$; $b = 1{,}5070$; temp. = 91° C

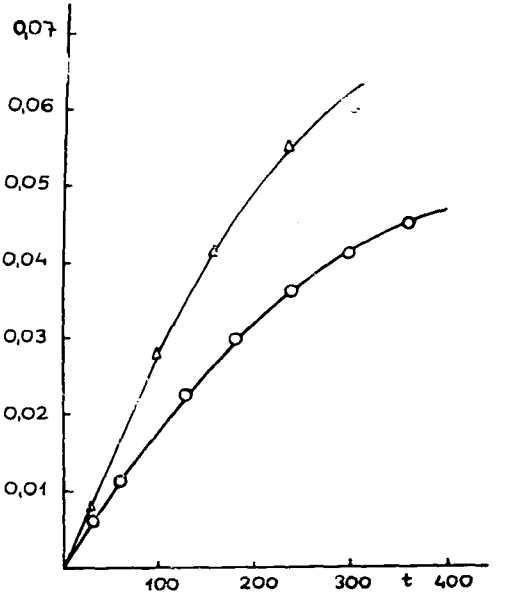

Fig. 5.

○ : $a = 0{,}100$; $b = 0{,}8933$;
△ : $a = 0{,}100$; $b = 1{,}0330$
H_2O : 2% ; (temp. = 71° C)

Rearrangement of (±) cis-2-benzamido-cyclohexan-1-ol

Measurements were carried out — in view of the low solubility of substrate — in the presence of about 1,7 mole/l of hydrogen chloride at 71° C, 81° C and 91° C. Rate constants and their mean values are summarized in Table III. The activation energy was found to be 15,8 Kcal/mole.

Experimental

Materials

Both of (±) cis- and trans-2-benzamido-cyclohexan-1-ol were prepared according to McCASLAND [10], then several times recrystallized from dioxan and held in desiccator filled with phosphorous pentoxide.

Dry dioxan was prepared from azeotropic aqueous dioxan [11]. Its purity was controlled by measuring the refractivity while its dryness checked by KARL FISCHER's reagent.

Dioxanic hydrogen chloride was prepared from dry dioxan by saturating with dry hydrogen chloride in the following way: dry dioxan was introduced into a flask provided with magnesium perchlorate protecting tube through which hydrogen chloride, formed from ammonium chloride, was bubbled. Previously this hydrogen chloride was carried through two towers filled with sulphuric acid and a column filled with phosphorous pentoxide. The hydrogen chloride content of dioxan was determined by titration and hydrogen chloride concentration applied at the measurements was adjusted from time to time by dilution of it with dry dioxan. Both dioxan and dioxanic hydrogen chloride were held in waxed glass vessel to keep off wetting.

To controll the dryness of dioxanic hydrogen chloride (*e.g.* with KARL FISCHER's reagent) did not succeed.

Materials consumpted by the determination of nitrogen with HUSSEY—MAURER's [12] apparatus were all of corresponding to the description of authors mentioned quality.

Measurements

Solutions of different concentrations were all prepared so that samples were weighed into a 50 ml. containing volumetric flask, solved in dioxanic hydrogen chloride at room temperature, then filled to the mark. After the stock solution was prepared, the ground-glass stopper of the flask was replaced by a groundglass stopper of an authomatic buret of 10 ml capacity divided into 0,02 ml and provided with a drying tube (P_2O_5). In the place of the outlet there was a glass capillar, pulled to 10 cm out, connected with the buret with a rubber tube closed by a glass-bead. The solution was measured by 5 mls into glass balls of 10 ml volume. They were immediately soldered, care was taken to prevent loss of hydrogen chloride. In the residue of the solvent hydrogen chloride content was titrimetrically determined and this was considered to be the initial concentration of hydrogen chloride. The soldered balls were placed into Höppler thermostat set in at corresponding temperature so that they suspended on a thread into the liquid of the inner vessel of the thermostate. The replacing of the cover of thermostate was considered as the starting point of the reaction. At corresponding intervals a ball was taken out and immediately sunk into salted ice where the reaction mixture shortly freezed. The placing into the ice was considered as the end point of the reaction. Balls taken out of ice and carefully cleaned were

smashed in a flask containing 5 ml water and after shaking, a corresponding amount was pipetted out from the solution, its nitrogen content determined in a Hussey—Maurer apparate [12].

* * *

The author wishes to express his gratitude to G. FODOR, member of the Hungarian Academy of Sciences and É. FODOR—VARGA for their kind interest in this work and also for their valuable advices.

References

[1] *Böttchner, W.:* Ber. dtsch. chem. Ges. **16**, 629 (1883).
[2] *v. Auwers, K.:* Annalen **32**, 159 (1904).
[3] *Bergmann, E.:* Ber. dtsch. chem. Ges. **54**, 936 (1921).
[4] *Bergmann, M., H. Brand:* Ibid. **56**, 1280 (1923).
[5] *Bruckner, V.:* Annalen **518**, 226 (1933).
[6] *Welsh, L. H.:* J. Amer. Chem. Soc. **71**, 3500 (1949).
[7] *McCasland, G. E., D. E. Smith:* J. Amer. Chem. Soc. **73**, 2195 (1951).
[8] *Fodor-Varga, É.:* Unpublished work.
[9] *Fodor, G., É. Fodor Varga, Á. Furka:* Croat. Chem. Acta **29**, 303 (1957).
[10] *McCasland, G. E., R. K. Clark, E. Carter:* J. Amer. Chem. Soc. **71**, 637 (1949).
[11] *Pestemer, M.:* Angew. Chem. **63**, 118 (1951).
[12] *Hussey, A. S., J. E. Maurer:* Anal. Chem. **24**, 1462 (1952).